Original Article

Relative Effectiveness of Adjuvant Chemotherapy for Invasive Lobular Compared With Invasive Ductal Carcinoma of the Breast

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BACKGROUND: Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) have distinct clinical, pathologic, and genomic characteristics. The objective of the current study was to compare the relative impact of adjuvant chemotherapy on the survival of patients with ILC versus those with IDC. **METHODS:** Women with *estrogen receptor* (ER)-positive, *human epidermal growth factor receptor 1* (HER2) -negative, stage I/II IDC and ILC who received endocrine therapy were identified from the 2000 to 2014 California Cancer Registry. Patient, tumor, and treatment characteristics were collected. Ten-year overall survival (OS) was estimated using the Kaplan-Meier method and Cox proportional-hazards modeling. **RESULTS:** In total, 32,997 women with IDC and 4638 with ILC were identified. The receipt of chemotherapy significantly decreased during the study for both subtypes. For patients with IDC, the 10-year OS rate was 95% among those who received endocrine therapy alone versus 93% ($P<.01$) among those who received endocrine therapy plus chemotherapy. For patients with ILC, the 10-year OS rate was 94% among those who received endocrine therapy alone versus 92% ($P<.01$) among those who received endocrine therapy plus chemotherapy. After adjusting for patient and treatment factors, adjuvant chemotherapy was significantly associated with a decreased 10-year hazard of death for patients with IDC (hazard ratio, 0.83; 95% confidence interval, 0.74-0.92). In contrast, adjuvant chemotherapy was not independently associated with the adjusted 10-year hazard of death for patients with ILC (hazard ratio, 1.14; 95% confidence interval, 0.90-1.46). **CONCLUSIONS:** Adjuvant chemotherapy was not associated with improved OS for patients with *ER-positive*, *HER2-negative*, stage I/II ILC. Avoidance of ineffective chemotherapy will markedly reduce the adverse effects and economic burden of breast cancer treatment for a large proportion of patients with breast cancer. ***Cancer*** **2017;123:3015-21.** *© 2017 American Cancer Society.*

KEYWORDS: chemotherapy, breast cancer, endocrine therapy, invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), survival.

INTRODUCTION

Invasive lobular carcinoma (ILC) is the second most common histologic subtype of breast cancer and comprises from 5% to 15% of all breast cancers.[1] ILC differs from invasive ductal carcinoma (IDC) (the most common histologic subtype) with respect to epidemiology, clinicopathologic features, genomic profile, and response to treatment. Classical ILC is characterized by small, uniform, noncohesive cells that infiltrate the stroma in a single-file pattern. Compared with IDC, classical ILC is almost always *estrogen receptor* (ER)-positive and *human epidermal growth factor receptor 2* (HER2)-negative.[2] Because of their noncohesive growth pattern, ILCs are more difficult to detect on mammography.[3] In addition, ILCs are uniquely more likely to metastasize to peritoneal surfaces.[2]

The genomic profile of ILCs is also different from that of ER-positive/HER2 negative IDCs. The 21-gene recurrence scores (RS) for ILCs are rarely categorized as high risk, whereas approximately 8% to 15% of ER-positive/HER2-negative IDCs are categorized as high risk.[4-6] In addition, the pathologic complete response (pCR) rates after neoadjuvant chemotherapy are substantially lower for ILC compared with *ER-positive/HER2-negative* IDC.[7-11] Also, the relative effectiveness of letrozole compared with tamoxifen is higher for ILC versus IDC.[12]

Despite the unique molecular and clinical properties of ILCs, published randomized clinical trials evaluating the effectiveness of adjuvant chemotherapy for *ER-positive* breast cancer have not reported outcomes separately based on histologic subtype. Furthermore, current guidelines do not consider histologic subtype as a factor for determining the receipt of adjuvant chemotherapy for *ER-positive/HER2-negative*, stage I/II breast cancer.[13,14] On the basis of the genomic profile of ILC and the very low rates of pCR to neoadjuvant chemotherapy, we hypothesized that adjuvant chemotherapy is associated with minimal added benefit for patients with stage I/II ILCs who receive endocrine therapy. Our objective was to

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characterize the factors associated with chemotherapy receipt and to determine the relative impact of adjuvant chemotherapy on the survival of patients with ILC and IDC.

MATERIALS AND METHODS

Data

We used California Cancer Registry (CCR) data from 2000 to 2014 to identify women who had IDC and ILC (defined according to the Surveillance, Epidemiology, and End Results program of the National Cancer Institute; International Classification of Diseases-03 histology codes 8500 and 8520 for IDC and ILC, respectively). Cases are reported to the Cancer Surveillance Section of the California Department of Public Health from hospitals and any other facilities providing care or therapy to patients with cancer who reside in California.[15] The CCR collects patient, tumor, and treatment characteristics, including age at diagnosis, race, socioeconomic status (SES), primary tumor site, tumor histologic subtype, tumor stage, tumor grade, *ER* status, *progesterone receptor* (PR) status, *HER2* status, surgery type, receipt of chemotherapy and endocrine therapy, receipt of radiation, vital status, and cause of death.[15] SES information was reported by the CCR at the aggregate level and was used as a surrogate for individual level data. Our study was exempt from review by the Human Subjects Committee of the University of Minnesota's Institutional Review Board, because it used a de-identified data source.

Patients

We included women who were diagnosed between 2000 and 2014 and who underwent surgical resection and received adjuvant endocrine therapy. We excluded patients aged ≥75 years and those who were diagnosed outside of California, while in a nursing home, by autopsy, or on death certificate. We also excluded women who had multiple primary breast cancers diagnosed in a lifetime and those who had the following tumor characteristics: tumor grade 4, tumor stage III or IV, positive *HER2* status, *HER2* status unknown, negative *ER* status, and *ER* status unknown. Although the CCR includes patients with grade 4 disease, the small cohort of patients who had grade 4 tumors were excluded from the final analyses, because this is not a typical classification for breast cancers and may represent coding misclassification. We also specifically excluded patients for whom receipt of endocrine therapy was unknown and those who had mixed ductal and lobular carcinoma. After all of the above exclusions, we created 2 cohorts of patients with either IDC or ILC.

TABLE 1. Description of Patients With Invasive Ductal and Lobular Carcinoma: California Cancer Registry, 2000-2014

Characteristic	No. of Patients (%)	
	IDC	ILC
Total	32,149 (100)	4095 (100)
Year of diagnosis		
2000-2002	4475 (14)	435 (11)
2003-2005	5487 (17)	612 (15)
2006-2008	8380 (25)	1024 (25)
2009-2011	8202 (25)	1121 (27)
2012-2014	6060 (19)	903 (22)
Age, y		
18-44	4021 (12)	256 (6)
45-54	8881 (27)	1038 (25)
55-64	10,690 (33)	1467 (36)
65-74	9012 (28)	1334 (33)
Socioeconomic status		
Low	5276 (16)	635 (15)
Middle	9391 (29)	1218 (30)
High	6348 (19)	970 (24)
Missing	11,589 (36)	1272 (31)
Race		
Non-Hispanic white	21,450 (66)	2941 (72)
Black	1516 (5)	188 (5)
Other	9638 (29)	966 (23)
Tumor grade		
1	10,361 (32)	1505 (37)
2	16,112 (49)	2325 (57)
3	6131 (19)	265 (6)
Tumor stage		
I	20,742 (64)	2047 (50)
II	11,862 (36)	2048 (50)
Tumor PR status		
Positive	5294 (16)	532 (13)
Negative	787 (3)	97 (2)
Unknown	26,523 (81)	3466 (85)
Radiation		
No	9516 (29)	1543 (38)
Yes	23,088 (71)	2552 (62)
Surgery type		
Partial mastectomy	23,241 (71)	2366 (58)
Unilateral mastectomy	7403 (23)	1268 (31)
Bilateral mastectomy	1960 (6)	461 (11)
Adjuvant chemotherapy		
No	21,323 (65)	2748 (67)
Yes	11,281 (35)	1347 (33)

Abbreviations: IDC, invasive lobular carcinoma; ILC, invasive lobular carcinoma; PR, progesterone receptor.

Statistical Analysis

We evaluated the unadjusted differences between demographic and treatment characteristics among the patients in our 2 cohorts. We then used multivariable logistic regression to evaluate the relation between patient, tumor, and treatment characteristics and the receipt of adjuvant chemotherapy. Overall survival (OS) was analyzed using both Kaplan-Meier methods and Cox proportional-hazards modeling. All models included the year of diagnosis, patient age, SES (low, middle, high, or missing), race (non-Hispanic white, black, or other), tumor grade

TABLE 2. Factors Associated With the Receipt of Adjuvant Chemotherapy for Invasive Ductal Carcinoma (Model 1) and Invasive Lobular Carcinoma (Model 2): California Cancer Registry, 2000-2014

	Model 1: IDC		Model 2: ILC	
Factor	OR	95% CI	OR	95% CI
Year of diagnosis				
2000-2002	Ref		Ref	
2003-2005	1.16	1.01-1.35[a]	0.94	0.64-1.38
2006-2008	0.95	0.75-1.20	0.39	0.22-0.71[a]
2009-2011	0.68	0.54-0.86[a]	0.29	0.16-0.51[a]
2012-2014	0.52	0.41-0.66[a]	0.15	0.08-0.26[a]
Age, y				
18-44	Ref		Ref	
45-54	0.46	0.41-0.66[a]	0.71	0.50-0.98[a]
55-64	0.22	0.20-0.25[a]	0.31	0.22-0.42[a]
65-74	0.08	0.07-0.09[a]	0.11	0.07-0.16[a]
Socioeconomic status				
Low	Ref		Ref	
Middle	0.89	0.81-0.99[a]	0.95	0.74-1.23
High	0.81	0.72-0.91[a]	0.87	0.66-1.13
Missing	0.88	0.74-1.04	0.76	0.50-1.14
Race				
Non-Hispanic white	Ref		Ref	
Black	0.90	0.78-1.05	0.82	0.55-1.22
Other	1.16	1.07-1.27[a]	1.07	0.88-1.29
Tumor grade				
1	Ref		Ref	
2	2.16	2.00-2.34[a]	1.64	1.38-1.96[a]
3	6.31	5.73-6.96[a]	2.17	1.57-2.99[a]
Tumor stage				
I	0.10	0.09-0.11[a]	0.13	0.11-0.16[a]
II	Ref		Ref	
Tumor PR status				
Positive	Ref		Ref	
Negative	0.88	0.71-1.09	1.31	0.76-2.24
Unknown	0.87	0.75-1.02	1.34	0.91-1.99
Radiation				
No	Ref		Ref	
Yes	0.59	0.53-0.66[a]	0.55	0.44-0.69[a]
Surgery type				
Partial mastectomy	Ref		Ref	
Unilateral mastectomy	1.79	1.60-2.02[a]	2.35	1.86-2.96[a]
Bilateral mastectomy	2.01	1.72-2.36[a]	2.59	1.92-3.50[a]

Abbreviations: CI, confidence interval; IDC, invasive lobular carcinoma; ILC, invasive lobular carcinoma; OR, odds ratio; PR, progesterone receptor; Ref, reference category.
[a] This value indicates a statistically significant difference.

(1-3 and unknown), tumor stage (I and II), receipt of radiation, surgery type, and receipt of adjuvant chemotherapy. All statistical analyses were completed using SAS software, version 9.3 (SAS Institute, Cary, NC). The results were identified as statistically significant only at a $P \leq .05$, corresponding to a 95% confidence interval (CI).

RESULTS

Patient Population

In total, 32,149 patients with IDC and 4095 patients with ILC were identified in the CCR who underwent surgical resection and received adjuvant endocrine therapy (Table 1). The majority of patients in both groups were non-Hispanic white, had received treatment with endocrine therapy alone, had received radiation therapy, had grade 1 or 2 cancer, were aged > 55 years, and had undergone partial mastectomy.

Factors Associated With Adjuvant Chemotherapy Receipt for IDC and ILC

We identified several factors that were significantly associated with receipt of adjuvant chemotherapy (Table 2). The receipt of chemotherapy significantly decreased over time ($P \leq .05$) for both IDC and ILC. We then specifically investigated each histologic subtype independently and observed that, when adjusted for patient, tumor, and treatment characteristics, year of diagnosis (2006 and later), age ≥ 45 years, SES (middle and high vs low), receipt

of radiation, and stage I disease were significantly associated ($P \leq .05$) with nonreceipt of adjuvant chemotherapy for IDC (Table 2, model 1). Surgery type (unilateral and bilateral mastectomy vs partial mastectomy) and tumor grade (2, 3, and unknown vs 1) were also significantly associated with receipt of adjuvant chemotherapy for IDC. For ILC, year of diagnosis (2006 and later), age > 45 years, receipt of radiation, and stage I disease were significantly associated ($P \leq .05$) with nonreceipt of adjuvant chemotherapy (Table 2, model 2). Surgery type (unilateral and bilateral mastectomy vs partial mastectomy), PR status (negative and unknown vs positive), and tumor grade (2, 3, 4, and unknown vs 1) were significantly associated with receipt of adjuvant chemotherapy.

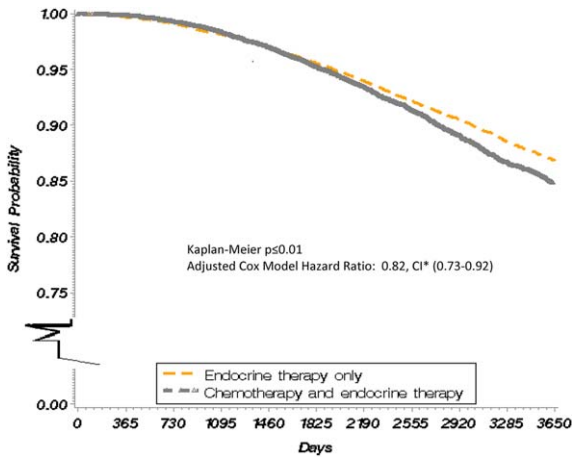

Figure 1. Ten-year Kaplan-Meier survival is illustrated for patients with invasive ductal carcinoma according to therapy type (n = 32,149). CI indicates confidence interval.

Factors Associated With Survival: IDC

For the IDC cohort, the unadjusted 10-year Kaplan-Meier OS rate was 87% for the endocrine therapy alone group versus 84% ($P < .01$) for the endocrine therapy and adjuvant chemotherapy group (Fig. 1). After adjusting for patient, tumor, and treatment characteristics, we observed a significant decrease in the 10-year hazard of death with the receipt of adjuvant chemotherapy in patients with IDC (hazard ratio [HR] 0.82; 95% CI, 0.73-0.92)

TABLE 3. Factors Associated With 10-Year Relative Hazard of Death: Cox Proportional-Hazards Models

	Model 1: IDC		Model 2: ILC	
Factor	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, y				
18-44	Ref			
45-54	0.96 (0.81-1.14)	.66	0.76 (0.43-1.32)	.34
55-64	1.30 (1.10-1.53)	.002[a]	1.12 (0.66-1.90)	.67
65-74	2.66 (2.26-3.12)	< .0001[a]	2.93 (1.74-4.52)	< .0001[a]
Socioeconomic status				
Low	Ref			
Middle	0.79 (0.68-0.92)	.005[a]	0.70 (0.49-0.99)	.04[a]
High	0.57 (0.47-0.68)	< .0001[a]	0.42 (0.27-0.65)	< .0001[a]
Missing	0.65 (0.48-0.86)	.002[a]	0.47 (0.23-0.96)	.04[a]
Race				
Non-Hispanic white	Ref			
Black	1.37 (1.16-1.61)	.0002[a]	1.19 (0.73-1.93)	.50
Other	0.98 (0.88-1.11)	.80	0.91 (0.69-1.21)	.52
Tumor grade				
1	Ref			
2	1.38 (1.24-1.54)	< .0001[a]	1.06 (0.83-1.34)	.65
3	2.25 (1.99-2.55)	< .0001[a]	1.49 (1.01-2.19)	.04[a]
Tumor stage				
I	Ref			
II	1.91 (1.72-2.10)	< .0001[a]	1.69 (1.31-2.19)	< .0001[a]
Radiation				
No	Ref			
Yes	1.18 (1.03-1.34)	.01[a]	1.06 (0.82-1.38)	.65
Surgery				
Partial mastectomy	Ref			
Unilateral mastectomy	1.23 (1.07-1.40)	.003[a]	1.53 (1.13-2.07)	.01[a]
Bilateral mastectomy	0.86 (0.61-1.21)	.86	0.80 (0.48-1.35)	.41
Adjuvant chemotherapy				
No	Ref			
Yes	0.82 (0.73-0.92)	.0004[a]	1.18 (0.90-1.54)	.21

Abbreviations: CI, confidence interval; HR, hazard ratio; IDC, invasive lobular carcinoma; ILC, invasive lobular carcinoma; Ref, reference category.
[a] This *P* value indicates a statistically significant difference.

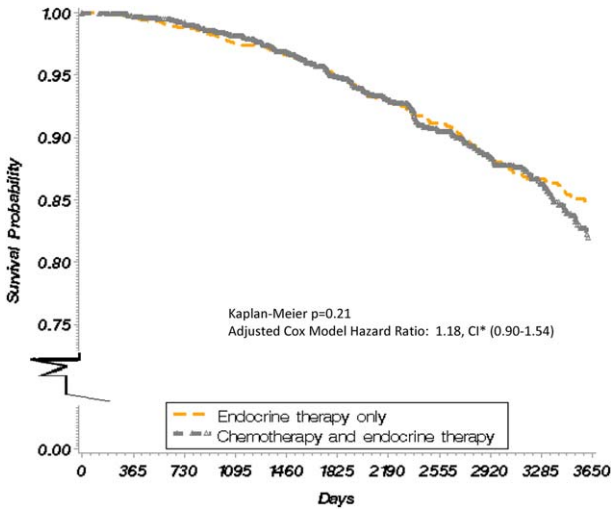

Figure 2. Ten-year Kaplan-Meier survival is illustrated for patients with invasive lobular carcinoma according to therapy type (n = 4095). CI indicates confidence interval.

(Table 3, model 1). Factors that were significantly associated with an increased hazard of death were older age (55 years vs 18-44 years; HR, 1.30; 95% CI, 1.10-1.53), receipt of radiation (HR, 1.18; 95% CI, 1.03-1.34), surgery type (unilateral mastectomy vs partial mastectomy: HR, 1.23; 95% CI, 1.07-1.40), tumor grade 2 and 3 (grade 2 vs 1: HR, 1.38; 95% CI, 1.24-1.54), and stage (stage II vs I: HR, 1.91; 95% CI, 1.72-2.10) (Table 3, model 1).

Factors Associated With Survival: ILC

For the ILC cohort, the unadjusted 10-year Kaplan-Meier OS rate was 84% for the endocrine therapy alone group and 83% ($P = .21$) for the endocrine therapy plus adjuvant chemotherapy group (Fig. 2). After adjusting for patient, tumor, and treatment characteristics, we did not observe a significant decrease in the 10-year hazard of death with the receipt of adjuvant chemotherapy for patients with ILC (HR, 1.18; 95% CI, 0.90-1.54) (Table 3, model 2). Factors that were significantly associated with an increased hazard of death were older age (≥65 years vs 18-44 years: HR, 2.93; 95% CI, 1.74-4.52), surgery type (unilateral mastectomy vs partial mastectomy: HR, 1.53; 95% CI, 1.13-2.07), tumor grade 3 (HR, 1.49; 95% CI, 1.01-2.19), and stage (stage II vs I: HR, 1.69; 95% CI, 1.31-2.19) (Table 3, model 2).

DISCUSSION

In this study using statewide data from California, we observed that the receipt of adjuvant chemotherapy significantly decreased in California during our study period for both ILC and IDC. Our data demonstrate that patients with *ER-positive*, *HER2-negative*, stage I/II ILC who received endocrine therapy did not benefit from the addition of adjuvant chemotherapy. In contrast, for patients with IDC, receipt of adjuvant chemotherapy was independently associated with an improved 10-year OS rate. These results suggest that ILC is a separate entity from *ER-positive/HER2-negative* IDC.

Prospective randomized trials comparing endocrine therapy alone versus endocrine therapy plus adjuvant chemotherapy for *ER-positive/HER2-negative* breast cancer have not reported outcomes separately based on histologic subtype. For example, in the National Surgical Adjuvant Breast and Bowel Project B-20 trial, combined adjuvant chemotherapy plus endocrine therapy was associated with improved survival compared with endocrine therapy alone for patients with *ER-positive* breast cancer.[16] However, the results from that study were not analyzed separately for patients with ILC. Similarly, an overview analysis from the Early Breast Cancer Trialists' Collaborative Group did not report survival outcomes after adjuvant therapy according to histologic subtype.[17] Neither the National Comprehensive Cancer Network nor the St Gallen International Expert Consensus guidelines consider histologic subtype as a factor for determining the use of adjuvant chemotherapy for early stage *ER-positive/HER2-negative* breast cancer.[13,14]

The observed differential survival outcomes of adjuvant chemotherapy based on histologic subtype in our study are consistent with the outcomes from several studies that have compared pathologic response rates to neoadjuvant chemotherapy between ILC and IDC. The pCR rate after neoadjuvant chemotherapy is about 0% to 5% for ILC compared with 9% to 20% for IDC.[7-11] In addition, the differential responsiveness of ILC and IDC to endocrine therapy alone was recently demonstrated in the prospective randomized Breast International Group 1-98 trial.[12] Compared with tamoxifen, letrozole significantly improved disease-free survival in patients with *ER-positive* ILC regardless of subtype (luminal A vs luminal B). After a median follow-up of 8.1 years, women with the luminal B subtype experienced a 60% risk reduction, whereas those with luminal A subtypes experienced a 55% risk reduction. For patients with IDC, treatment with letrozole impacted disease-free survival in the luminal B group only. These findings also suggest that ILC is not simply *ER-positive/HER2-negative* IDC.

Our findings are consistent with the results from another population-based study using the Netherlands Cancer Registry. Truin et al reported that adjuvant

chemotherapy was associated with improved 10-year survival rates for postmenopausal patients with IDC, but not for those with ILC.[18]

The lack of a survival benefit from the receipt of adjuvant chemotherapy for early stage ILC observed in our study is also consistent with the known genomic characteristics of this histologic subtype. The 21-gene RS is predictive of chemotherapy benefit for patients with *ER-positive/HER2-negative* breast cancer.[19] Several studies have evaluated the RS for both IDC and ILC. In 2 separate, single-center studies that included 108 patients[4] and 120 patients[5] with classical ILC, no patient was categorized in the high-risk group. In contrast, from 8% to 15% of patients with IDC were categorized as high risk.[6,14,20] Similarly, ILCs are much more likely to be categorized as "low risk" using the 70-gene MammaPrint genomic signature.[21] In addition, using genomic analysis, Desmedt et al observed that ILCs differed substantially from IDCs. Genes more commonly altered in ILC include the gene encoding for *E-cadherin* (CDH1), the genes involved in the *phosphatidylinositol 3 kinase* (PIK3) pathway (PIK3 *catalytic subunit* [PIK3CA], *phosphatase and tensin homolog* [PTEN], and *serine-threonine protein kinase 1* [AKT1]), the genes involved in the HER/Erb-B2 *receptor tyrosine kinase* (ERBB) pathway, and the *genes forkhead box 1A* (FOXA1) and *estrogen receptor 1* (ESR1).[22] Although it is not completely understood, this observed difference in genomic profiles of ILC compared with IDC likely underscores the attenuated response to adjuvant chemotherapy observed in patients with ILC.

We recognize several important limitations of this study. Because we used the CCR, the results of our study are limited to patients who received treatment in California. However, given the size and diversity of California, this limitation probably is not clinically meaningful. More important, the CCR does not report relevant information that may impact outcomes, including the proportion of ER positivity, results from genomic assays, patient comorbidities, specific endocrine therapy and chemotherapy regimens, and duration of such therapies. Also, the CCR does not report specific subtypes of ILC, such as pleomorphic lobular carcinoma, which may have improved outcomes with adjuvant chemotherapy. Finally, because this study used a cancer registry, patients were not randomly assigned to specific treatments.

Despite these limitations, our study is the largest report to date that specifically analyzes outcomes of patients with ILC who receive endocrine therapy with or without adjuvant chemotherapy. Controlling for patient age and tumor stage, we observed no survival benefit from adjuvant chemotherapy for patients with stage I/II ILC. These survival outcomes are consistent with the known genomic characteristics of ILC and the very low rates of pCR after neoadjuvant chemotherapy. The public health impact of this study is substantial, because ILCs represent about 10% of invasive breast cancers.[23,24] Because most patients have stage I or II disease, avoidance of ineffective chemotherapy will markedly reduce the adverse effects and economic burden of breast cancer treatment. Further research is necessary to identify specific subgroups of patients with ILC who might benefit from chemotherapy or targeted therapies.

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CONFLICT OF INTEREST DISCLOSURES

Natasha M. Rueth reports personal fees from Genomic Health. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Schelomo Marmor: Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–original draft, and visualization. **Jane Yuet Ching Hui**: Conceptualization, writing–original draft, writing–review and editing, and visualization. **Jing Li Huang**: Validation, visualization, and writing–review and editing. **Scott Kizy**: Validation, visualization, and writing–review and editing. **Heather Beckwith**: Validation, visualization and writing–review and editing. **Anne H. Blaes**: Validation, visualization, and writing–review and editing. **Natasha M. Rueth**: Validation, visualization, and writing–review and editing. **Todd M. Tuttle**: Conceptualization, methodology, validation, formal analysis, writing–original draft, writing–review and editing, supervision, project administration, and visualization.

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